REMARKS

Claim 7, 10, 12, 14-18, 20, 22-25 and 30-38 are currently pending. Claims 8, 11, 13, 19, 21 and 26-29 have been canceled.

It is asserted that claims 7 and 33-38 are drawn to distinct inventions. In view of the Restriction Requirement issued, claims 33-38 are thus withdrawn from consideration. However, Applicant notes that given claim 7 and claims 33-37 are related as product and process of use and that claim 7 and claim 38 are related as process of making and product made, claims 7 and 33-38 are subject to rejoinder in view of MPEP 821 upon indication of allowable subject matter with respect to claim 7.

1. The Rejections Under 35 U.S.C. §103(a)

Claims 7, 10, 15-18,20, 24, 25, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny et al. in view of Vogelstein et al.

The Office Action states:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use said cDNA to identify the genomic DNA that encodes the human MDM2 homolog of SEQ ID NO:2 on chromosome 12q12-14. The motivation is provided by Vogelstein et al. who teach that it binds to oncogene p53 and is diagnostic of tumorogenesis. The state of the art provides various techniques for obtaining genomic DNA using cDNA probes that are usually labeled. The comparison of genomic and cDNA would result in the identification of regions comprising exon-intron and intron-exon junctions within coding and non-coding regions. One of ordinary skill in the art would have been motivated to use said non-coding regions or fragments thereof of at least 20 nucleotides and up to 5000 or 51039 nucleotides (the entire length of SEQ ID NO:4) nucleotides for detecting splice variants of chromosome 12q12-14 from genomic nucleotide samples from an individual, for example. As a matter of convenience a non-coding region such as an exon-intron or intron-exon region or fragments thereof can be present in a kit or on a solid support. Further, said support can be a microarray according to a customary use of nucleic acid molecules in the art.

Applicant respectfully traverses the rejection. In Applicant's view, it would not have been obvious to combine the disclosure of Muzny and Vogelstein given that there was no suggestion to do so. Muzny merely contains just a small portion of chromosome 12 DNA.

Chromosome 12 is about 130 million base pairs long and is believed to contain several hundred genes (by analysis after 2001 and after the Applicant discovered the human MDM2 homologue gene). Muzny et al knew that clone AC025423 (from 1V11-61102) was from chromosome 12 but there is no evidence in the NCBI report of a sub-assignment to the p- or q-arm. Further, there is no evidence that Muzny et al. knew whether the clone did or did not contain one or more genes and particularly whether it contained the gene encoded by SEQ ID NO:4. Applicant notes that statements made by Justice Kennedy in *KSR v Teleflex*, 82 USPQ2d 1385; 127 S.Ct. 1727 (2007) are particularly pertinent. Specifically, the Court requires that, "[t]o facilitate review, the analysis should be made explicit,"; conclusory statements are not sufficient. No indication in the instant Office Action is provided as to how there would have been an apparent reason to combine these teachings.

Even assuming *arguendo* that there had been such a motivation, one of ordinary skill in the art would not have obtained the isolated nucleic acid molecules of the present invention, the specifically recited non-coding regions of the MDM2 gene located between nucleotides 20-51039 of SEQ ID NO:4. This is because, as noted in previous responses, Vogelstein et al. placed the human MDM2 homologue gene at 12q12-14. Actually, this finding is incorrect. After the publication of Vogelstein, the gene was found not[sic] to be located at 12q12-14, whereas the gene is actually several millions of base pairs away at 12q15. Thus, even if these two references were indeed combined, the ordinary skilled artisan would have looked for the MDM2 gene in the wrong location and thus would not have obtained the claimed sequences.

In response to Remarks made by Applicant in the amendment submitted on January 23, 2007, the Office Action states

> With regard to the 103(a) rejection, Applicant argues that "There was certainly no indication given in the cited art either singly or in combination regarding the location of the MDM2 gene encoding human mouse double minute 2 homolog depicted in SEQ ID NO:2 on AC025423" (Remarks, page 13). As was explained in the previous Office action mailed August 25, 2006 "the exact location of the gene is not necessary as long as its sequence is known as in the instant case" (page 5). At the time the invention was made finding non-coding regions using cDNA and genomic DNA was standard technique. Watson et al (1992) "Recombinant DNA teach that "once the first genes were cloned, introns were identified by comparing the cloned genomic DNA with the corresponding cloned cDNA (page 137, 2nd column). In the case of the instant

application, both genomic and cDNA were known. They only needed to be compared in order to identify intron-exon junctions. Applicant further argues that "There is no prior art that defines the complete genomic structure of a particular gene. This is necessary in order to identify the claimed noncoding sequences in the instant invention" (page 13). This argument is similar to the issue of location and is responded above. Applicants further argues that "One of ordinary skill in the art would have no idea as to the number of introns and the length of the 5' and 3' noncoding sequences in the MDM2 gene" (page 14). It is agreed that said number and length were not known before the invention. If they were known, the rejection would be 102. The current rejection is 103(a) stating that it would have been obvious to compare genomic DNA and cDNA and identify the number of introns and the length of the 5' and 3' noncoding sequences in the MDM2 gene. Applicant further argues "The Examiner's assertion that one of ordinary skill in the art would have expected that the location is often imprecise actually further supports Applicant's assertion the claimed sequences were indeed nonobvious. If the location is imprecise, where would one of ordinary skill in the art know where to look?" (page 15). This is not persuasive because the precise location is not necessary when the 2 sequences that need to be compared are known. They would be obvious because the genomic DNA was already sequenced and cDNA was made. Applicant further argues that "It should be noted that annotation of the human genomic DNA was still relatively new as of the priority date of the instant application. Even assuming arguendo that finding noncoding regions using cDNA and genomic DNA was standard technique, the means to make the invention does not predict the claimed invention. Specifically the means used to make the invention do not predict the claimed nucleic acid molecules. BLASTN, TBLASTN, etc. do not themselves predict gene-specific results. It is Applicant's view that only general guidance is provided. This is not sufficient" (page 16). This is not persuasive because there is no need to predict the sequence itself, it was known before. The invention is in the identification of the specific fragments (exons/introns) of the known sequence. Applicant appears to argue as if the genomic DNA was not sequenced prior to the instant invention. Applicant further argues that "it is Applicant's view that given that the cDNA constitutes just 1.6% of the AC025423 sequence is in itself evidence of the unpredictability of determining the entire sequence of the MDM2 gene and thus contiguous intron-exon and exon-intron regions. The Examiner is in effect asserting that just because Applicant did isolate the claimed nucleic acid molecule, it must have been obvious to do so. It is well established case law that the fact that the inventors were ultimately successful

> is irrelevant to whether one of ordinary skill in the art at the time the invention was made would have reasonably expected success" (paragraph bridging pages 16-1 7). This is not persuasive because the size of the cDNA does not matter. ESTs of smaller size are used for comparison to genomic sequences. Applicant does not show what unexpected difficulties other than routine comparison of the genomic DNA and cDNA were encountered during the time the invention was made.

It appears that the Examiner is asserting that just because a genomic clone containing chromosome 12 sequences had been isolated, the MDM2 cDNA was known and that techniques were known for finding noncoding regions, one of ordinary skill in the art would have had a reasonable expectation of success of obtaining the claimed sequences. Further, the Examiner is asserting that it is not significant that cDNA just constitutes just 1.6% of the AC025423 sequence. Applicant disagrees for a number of reasons.

First, Applicant takes issue with the assertion made with respect to Watson, 1992. Specifically, Watson specifically states on page 137

> It should be noted that at the time that the electron microscopy experiments on adenovirus were done, no one had clone a cellular gene yet. Once the first genes were cloned, introns were identified by comparing the cloned genomic DNA with the corresponding cloned cDNA.

This is very different from the situation with respect to the isolated non-coding fragments of the instant invention. Muzny et al. merely discloses the sequence of a genomic clone containing chromosome 12 sequences, not isolated SEQ ID NO:4. No indication is provided which portion of chromosome 12 is included. Vogelstein merely discloses the MDM2 cDNA. Applicant was the first to identify SEQ ID NO:4 and determine that it did indeed encode MDM2 and in particular determine the claimed noncoding sequences. Therefore, Watson, 1992 is not particularly pertinent.

Second, Applicant asserts that there would not be a reasonable expectation of success of obtaining the claimed noncoding sequences of SEQ ID NO:4 in view of the cited references. Vogelstein et al. placed the human MDM2 homologue gene at 12q12-14. As noted above, there was actually a previous disclosure stating that the MDM2 was located between 12q14.3-15 (see, for example, Andersen et al., 1996, Mammalian Genome 7:780-783 and Bureau, 1995, Genomics 28: 109-112, submitted and disclosed in previous response). However, given the conflicting locations published as of the priority date of the instant application, one of ordinary

skill in the art would not have known which location was actually correct. Actually, after the publication of Vogelstein, the gene was found no to be located at 12q12-14, whereas the gene is actually several millions of base pairs away at 12q15. Even assuming arguendo that it is well known in the art that the localization on the chromosome is often imprecise and one of ordinary skill in the art would have been motivated to search the cDNA sequence against the entire genomic DNA in order to find the identical regions, it is doubtful as to whether one of ordinary skill in the art would have had a reasonable expectation of success. The prior art disclosed two incorrect locations of the MDM2 gene. Given this situation, it is unlikely that one of skill in the art would have had a reasonable expectation of success of actually finding SEQ ID NO:4 and ultimately the noncoding sequences.

Third, Applicant takes issue with the assertion that it is not particularly relevant that the MDM2 cDNA merely constitutes 1.6% of AC025423 since size does not matter. Given the vast difference in size between the MDM2 cDNA and the AC025423, one of skill in the art, there would be an almost infinite number of possibilities with respect to reading frames and splice site possibilities regarding the location of SEQ ID NO:4 and particularly MDM2 noncoding sequences. In this case, undue experimentation would be involved and there could not be a reasonable expectation of success. It would thus follow that this could still constitute an obvious to try situation even in view of *KSR v Teleflex*, 82 USPQ2d 1385; 127 S.Ct. 1727 (2007). It is stated in KSR that

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103. *id*

Thus, under KSR, an approach that is obvious to try is also obvious where normal trial and error procedures will lead to the result. In Applicant's view, normal trial and error does not apply where the cDNA merely constitutes 1.6% of the AC025423 and there is no indication that AC025423 actually contains the claimed sequences. This situation in Applicant's view would constitute undue experimentation.

In view of the above arguments and the amendments of claims 7 and 24, Applicant asserts that the rejections under 35 USC 103 have been overcome. Therefore, Applicant respectfully requests that the rejection be with withdrawn.

7. Conclusion

In view of the foregoing, Applicants assert that the claims are now in condition for allowance. Early action to that end is respectfully requested. The Examiner is invited to contact the undersigned at (914) 712-0093 if she has any questions.

Respectfully submitted,

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